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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/829,201	04/22/2004	Daniel J. Drucker	016777-0616	5544

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EXAMINER	
JIANG, DONG	
ART UNIT	PAPER NUMBER
1646	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/829,201	DRUCKER ET AL.	
	Examiner	Art Unit	
	Dong Jiang	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *7-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-11* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/22/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Applicant's election with traverse of Group I ivention, claims 1-6, filed on 05 February 2007 is acknowledged. The traversal is on the ground(s) that Groups I-III are classified in the same class and subclass, therefore, one search of the identified class and subclass would encompass all of Groups I-III, and that, according to MPEP, in a proper requirement for restriction, an explanation showing why there would be a serious burden on the examiner must be shown, which is absent in the restriction requirement. This is not found persuasive because, according to MPEP (§808.02 [R-5]), a serious burden may be established by any *one* of the following: (A) separate classification thereof; (B) a separate status in the art when they are classifiable together; or (C) a different field of search. In the instant case, although the groups are in the same classification, they are independent or distinct inventions, and each group has a separate status in the art, and requires a different field of search. For example, diseases of the GI tract (those in claim 9 of invention II, for example) and conditions requiring suppress appetite (obesity in claim 11 of invention III, for example) involve different causes, different patient populations, have distinct clinical and pathological manifestations, require different methods of diagnosis and treatment, and have distinct features in progress and prognosis. Therefore, each group has a separate status in the art, and requires a different field of search of the prior art, and search all groups constitute serious burden. Further, a search for one group may reveal overlapping information about the other group, however, a search is aimed to find references that would render the invention obvious, as well as references directed to anticipation of the invention. Therefore, a search for one group is not adequate as to revealing references anticipating the other groups. For example, a search of GLP-1 and GLP-2 do not necessarily reveal anticipating art for a method for treating diseases/conditions recited in claims 9-11. Thus, independent searches of relevant literature in different areas of subject matter are required for different groups, which constitute undue burden.

The requirement is still deemed proper and is therefore made FINAL.

Note, the examiner also indicated in the restriction requirement that where applicant elects claims directed to the product, and a product claim is subsequently found allowable,

withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996).

Currently, claims 1-11 are pending, and claims 1-6 are under consideration. Claims 7-11 are withdrawn from further consideration as being drawn to a non-elected invention.

Formal Matters:

Information Disclosure Statement

Applicant's IDS submitted on 4/22/04 is acknowledged and has been considered. A signed copy is attached hereto.

Priority acknowledgement

This application lacks the necessary reference to the prior application. A statement reading "This is a continuation of Application No. 10/060,279 filed on 2/1/02, now abandoned, which claims benefit of U.S. provisional application No. 60/265,329 filed on 2/1/01." should be entered following the title of the invention or as the first sentence of the specification.

Rejections under 35 U.S.C. §112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because the term "a pharmaceutical combination" is vague, as "combination" is not a specific term for compositions, and could be used for agents physically separated. Therefore, it cannot be determined whether the claim is drawn to a composition of a kit. "A pharmaceutical *composition*" would be remedial. The claim is further indefinite for the recitation "a GLP-2 activity" and "a GLP-1 activity" because it is unclear what GLP-2 activity or GLP-1 activity is intended, and the specification does not define such. Thus, the metes and bounds of the claim cannot be determined. Claim 6 is indefinite for the recitation "a pharmaceutical combination".

Claim 6 is further indefinite because a kit claim, by definition, must contain two or more elements, and the interrelationships between the elements must be explicitly stated (see *In re Venezia*, 530 USPQ 2d 956 (CCPA 1975)). Instructional material is not given weight as an element, therefore, the claim is an improper kit claim as it requires at a minimum only the composition and instructions. Further, a kit usually comprises *a compartment* containing the product(s). In the instant case, it is unclear what is the interrelationship between the compartment and the composition, and whether one or two compositions are intended.

The remaining claims are included in this rejection because it is dependent from the specifically mentioned claims without resolving the indefiniteness issue belonging thereto.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited in scope to a pharmaceutical composition comprising a GLP-2 receptor agonist and a GLP-1 receptor antagonist, and a kit thereof, for the use of reducing or inhibiting food intake or suppressing appetite in mice, does not reasonably provide enablement for claims to a pharmaceutical combination comprising any GLP-2 activity enhancer and any GLP-1 activity inhibitor, useful *to treat or to inhibit the onset of a medical condition for which treatment with GLP-2 is indicated,* or for *preventing the onset of the medical condition* (claims 1 and 6, for example). The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with the claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The independent claim 1 is directed to a pharmaceutical combination comprising a GLP-2 activity enhancer and a GLP-1 activity inhibitor, wherein the combination is useful to treat or to inhibit the onset of a medical condition for which treatment with GLP-2 is indicated.

With respect to the limitation "useful to treat or to inhibit the onset of a medical condition for which treatment with GLP-2 is indicated" in claim 1, it reads on treating and *preventing* (inhibit the onset") any or all conditions/diseases associated to the GLP-2 treatment. However, the specification merely discloses one condition, food intake, in mouse models (wild type and GLP-1R-/-), which demonstrate that the inhibitory effects of *icv* (intracerebroventricular) $hGly^2GLP-2$ (a GLP-2 analogue) on food intake were significantly more pronounced when co-administered with a GLP-1 receptor antagonist, exendin(9-39) in comparison to the effects by $hGly^2GLP-2$ alone (wildtype mice), and that GLP-1R-/- mice exhibited a significantly greater sensitivity to the inhibitory actions of the GLP-2 on food intake (pages 22-23). The results indicate that inhibition of GLP-1 receptor signaling using peptide antagonists, or using a genetic approach to disrupt GLP-1 receptor expression is associated with enhancement of GLP-2 action *in the CNS on food intake* (page 23). However, such indication has not shown or tested in any other system or condition where treatment of GLP-2 is indicated. Further, the unpredictability in this field is indicated in the prior art. For example, contrary results have been reported by Tang-Christensen et al. (Nature Medicine, 2000, 6(7): 802-807, provided by applicants) using a rat model. Tang-Christensen teaches that prior central administration of exendin(9-39) completely reversed the GLP-2-induced anorexia, and food intake in the treated animals returned to the same level as that in the control animals (page 803, the first paragraph of the right column), indicating that exendin(9-39) is a functional GLP-2 antagonist in vivo. It seems that the GLP-1 receptor antagonist, exendin(9-39), when used with GLP-2 centrally, has completely different effects on

GLP-2-induced anorexia in mice and rats, which are both murine species. Furthermore, the prior art, as cited by applicants on page 24 of the specification ([0061]) also indicates the inhibitory effect of GLP-1 agonists on food intake in mice, rats and human. As such, one of skilled in the art would not be able to extrapolate whether a GLP-1 receptor antagonist would be effective on enhancing GLP-2-induced anorexia in human or any other species, nor to draw any conclusion from the results of the two model systems. The specification provides no instruction/guidance, nor working example as to what effect a GLP-1 receptor antagonist would have on GLP-2-induced anorexia in human or animals other than mice; whether GLP-1 receptor agonists would have additive or contradictory effect on reducing food intake when used with GLP-2 receptor agonist (based on the results of prior art); and what effect a GLP-1 receptor antagonist would have on other actions of GLP-2, independent of its anorexia effect, such as the intestinotrophic property. Therefore, it is highly unpredictable as to what effect a GLP-1 receptor antagonist would have with respect to GLP-2-induced anorexia when it is applied to other animals such as human, what effect a GLP-1 receptor antagonist would have on other actions of GLP-2, and whether the claimed pharmaceutical combination is suitable for any medical condition/disease other than for reducing food intake. As such, undue experimentation would be required to determine such prior to treating any diseases or conditions as claimed.

Due to the large quantity of experimentation necessary to determine the biological effects of a GLP-1 receptor antagonist on other actions of GLP-2 in any or all subjects; the lack of direction/guidance presented in the specification regarding same; the absence of working examples directed to same; the extremely complex nature of the invention; the state of the prior art that demonstrated contrary results in closely related animal model, and the anorectic effect of GLP-1 agonists; and the breadth of the claims embrace a broad class of diseases or disorders, and a broad class of genus of subjects being treated, undue experimentation would be required of the skilled artisan to make the claimed invention in its full scope.

With respect to the limitations of "to *inhibit the onset* of a medical condition" in claim 1, and "preventing the onset of said medical condition" in claim 6, which read on *preventing* a disease, the specification merely teaches the inhibiting effect on food intake or appetite, and the prior art has not established that any of the diseases can be prevented as claimed. All that has been shown is that the diseases can be treated. To prevent the onset of a disease, or to treat an

individual at risk of developing a disease would necessarily mean that an individual would have to be first identified as at the risk before the disease develops, and then given said combination, and such administration would ensure that the individual did not develop the disease. As neither the prior art nor the specification has established how to identify individuals who are at risk of developing a disease, the use of the pharmaceutical combination for inhibiting the onset of a medical condition is not enabled void. For the reasons above, elimination of the intended use would be remedial.

With respect to the limitation "a GLP-2 activity enhancer and a GLP-1 activity inhibitor" in claims 1, as no structural limitations required, the claim reads on any or all functional equivalents of the "enhancer" or the "inhibitor". However, the specification discloses merely *one* type of "GLP-2 activity enhancer", namely GLP-2 receptor agonist, which is represented by one molecule, human Gly^2GLP-2; and *one* type of "GLP-1 activity inhibitor", namely GLP-1 receptor antagonist, which is represented by one molecule, exendin(9-39). The specification does not teach any other biological equivalents of "a GLP-2 activity enhancer" or "a GLP-1 activity inhibitor", nor instruction/guidance or working example regarding how to make all functional equivalents of the "enhancer" or "inhibitor". For instance, a GLP-2 polynucleotide for gene therapy would be "a GLP-2 activity enhancer", an antisense nucleotide of GLP-1 would be "a GLP-1 activity inhibitor" (the instant claim reads on such for the gene therapy), or a give small chemical molecule with the recited functional activity. Therefore, the specification does not reasonably provide enablement commensurate in scope with claim, and it would require undue experimentation to make the invention in a manner commensurate in scope with the claim.

Due to the large quantity of experimentation necessary to identify the structure and activity of additional functional equivalents of the "enhancer" or the "inhibitor", the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art that has not established that biological equivalents can be predicted based on the structure of one molecule, and the breadth of the claims which fail to define the structures of the molecules and embrace a broad class of functional equivalents, undue experimentation would be required of the skilled artisan to make the claimed invention in its full scope.

Claims 1-6 are further rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is directed to a pharmaceutical combination comprising a GLP-2 activity *enhancer* and a GLP-1 activity *inhibitor* (note: some of the dependent claims merely define either "enhancer" or "inhibitor", but not both), and claim 6 is directed to a kit thereof. The terms "enhancer" and "inhibitor" in the claim read on any or all functional equivalents thereof, without any structural limiation. However, the specification discloses merely *one* type of "a GLP-2 activity enhancer", namely GLP-2 receptor agonist, which is represented by one molecule, human Gly^2GLP-2; and *one* type of "a GLP-1 activity inhibitor", namely GLP-1 receptor antagonist, which is represented by one molecule, exendin(9-39), and no other "enhancer", "inhibitor", GLP-2 receptor agonist, or GLP-1 receptor antagonist meeting the limitations of the claim is identified or particularly described.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the GLP-2 receptor agonist Gly2GLP-2, and the GLP-1 receptor antagonist exendin(9-39), the skilled artisan cannot envision the detailed chemical structure of the encompassed "enhancer" and "inhibitor" (claim 1, for example), "a GLP-2 receptor agonist" (claim 2, for example), and "a GLP-1 receptor antagonist" (claim 4, for example), and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, no GLP-2 activity enhancer except the GLP-2 receptor agonist Gly2GLP-2, and no GLP-1 activity inhibitor except the GLP-1 receptor antagonist exendin(9-39) meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Prior Art:

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Tang-Christensen et al. (Nature Medicine, 2000, 6(7):802-807, provided by applicants) teaches that prior central administration of a GLP-1 receptor antagonist, exendin(9-39), completely reversed the GLP-2-induced anorexia, and food intake in the treated animals return to the same level as that in the control animals (page 803, the first paragraph of the right column).

Gutzwiller et al. (Am J Physiol. 1999 May;276(5 Pt 2):R1541-4, cited by applicants, reference# 49) teaches that intravenous infusion of GLP-1 reduces appetite in type II diabetic patents, suggesting that GLP-1 has a role in controlling appetite and energy intake in humans (abstract).

Thim et al. (US5,912,229) teaches the use of GLP-2 for suppressing appetite for the treatment of obesity or type II diabetes (abstract, and column 2, lines 51-52). Additionally, Thim teaches that GLP-2 may be combined with another appetite-suppressing or satiety-inducing agent such as GLP-1 (column 10, lines 38-41).

Conclusion:

No claim is allowed.

Advisory Information:

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 571-272-0872. The examiner can normally be reached on Monday - Friday from 9:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Dong Jiang, Ph.D.
Patent Examiner
AU1646
3/28/07